

**REMARKS**

Claims 9 - 19 are now in this application. Claims 1 - 8 are rejected. Claims 1 - 8 are cancelled herein, without prejudice. New claims 9 - 19 are added to clarify the invention, to express the invention in alternative wording, and to address matters of form unrelated to substantive patentability issues, so as to more particularly recite and distinctly claim the subject matter of the present application which the Applicants regard as the invention. As an example of matters of form, reference numerals are removed because the elements of the claims are not considered limited to specific corresponding structures in the drawings. Other formal matters are attended to that were not addressed by the Examiner and accordingly are considered unrelated to substantive patentability issues. No new matter is introduced by any of the new claims.

Applicant submits herewith a substitute specification and abstract wherein amendments are effected to place the text thereof into proper English in accordance with 37 CFR 1.125(c). Also accompanying this amendment is a reproduction of the original specification and abstract with markings indicating the amendments effected in the substitute specification in accordance with MPEP §608.01(q) and 37 CFR 1.125(b). No new matter is added. Entry of the substitute specification and abstract is respectfully requested.

In the Office Action, the Examiner indicated that Applicants' cited reference, entitled "DNA Amplification with a Microfabricated Reaction Chamber", cited in the application and Applicants' Information Disclosure Statement filed July 21, 2000, was not considered because a publication date was not provided for the reference.

Applicants have provided the following bibliographical information regarding this reference, which has also been inserted in the specification at page 2, lines 4 - 7 thereof, as part of the substitute specification provided herewith, by way of clarifying citation to that reference:

Northrup et al, DNA Amplification with a Microfabricated  
Reaction Chamber, 7th International Conference on Solid State  
Sensors and Actuators, Transducers Proceedings 93  
(June 1993, Yokohama, Japan), pp 924 -926

In view of the foregoing, it is respectfully submitted that this reference should now be considered by the Examiner.

In the Office Action, original claim 1 was objected to because it included reference characters not included within parentheses. This objection has been overcome by deleting reference in all the new claims submitted herewith as part of this Amendment to specific reference numerals in the drawings and specification, inasmuch, as stated above, Applicants do not wish that the scope of the claims

mistakenly be construed to be limited to the specific structures illustrated and described.

In the Office Action, original claims 1 - 8 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

The Examiner has indicated a number of specific bases, not repeated here, for rejection on account of the use of certain claim language that is indefinite and/or unclear.

All of the bases indicated by the Examiner are believed to have been overcome by the new claims presented herein above as part of this Amendment.

With regard to the Examiner's comments in the Office Action regarding the thermal conductivities referred to in original claim 1, and now in new claim 9, Applicants wish to point out that the previous phrase "a thermal conductivity as high as possible", regarding the thermal conductivity of the three substrate chips of the apparatus, has been written as "a thermal conductivity at least as high as that of silicon" in new claim 9; and the previous phrase "of poor thermal conductivity", regarding the thermal conductivity of the connecting chip of the apparatus, has been written as "having a thermal conductivity that is lower than the thermal conductivity of said substrate chips, and is at least as low as that of pyrex glass" in new claim 9.

Support for the above is found in the original specification at page 8, lines 24, 25, and page 9, lines 22 - 24, with respect to the former; and at page 6, lines 20, 21, and page 11, lines 11, 12, with respect to the latter. The foregoing also supports new claims 18 and 19.

All other bases for 35 U.S.C. 112, second paragraph rejections are believed to be overcome by the new claims, wherein all elements and terms are clearly defined, with appropriate antecedent bases provided as required, and all terms being used definitely and consistently throughout the new claims.

In the Office Action, original claims 1 - 8 were rejected under 35 U.S.C. 103 (a) as being unpatentable over U.S. Patent 5,534,328 to Ashmead et al ("Ashmead et al"), in view of U.S. Patent 5,875,385 to Stephenson et al ("Stephenson et al"), U.S. Patent 4,532,028 to Peterson ("Peterson"), or U.S. Patent 4,523,036 to Cornils et al ("Cornils et al").

The Examiner contends that, with regard to original claims 1, 2, 6, and 8 of the present application, Ashmead et al discloses a miniaturized chemical processing apparatus which is a substrate made up of a plurality of laminae, including wound flow paths (reference figs. 11 and 15) and subdivided flow paths (reference figs. 8, 9, 12, 16, and 17); laminae with heat exchangers (reference figs. 6, 10, 13, and 14); laminae with thermal barriers (reference figs. 9 and 12); and

inlets and outlets on each lamina so as to be aligned with their respective outlets and inlets in adjacent laminae (reference at col. 8, lines 41 - 54).

The Examiner then relies on the patentee's own self-serving and unsubstantiated statement in Ashmead et al (col. 5, line 56 - col. 6, line 7) regarding the alleged broad range of applicability and flexibility of the apparatus disclosed therein, to conclude and hold that it would have been obvious to a person of ordinary skill in the art at the time the present invention was made to configure the apparatus of that reference in such a way so as to be identical to the apparatus taught and claimed according to the present application, such that the apparatus featured enhanced safety and reduced capital investment (reference at col. 1, lines 9 -14).

The Examiner relies on Stephenson et al (fig. 1, col. 4, lines 4 - 9, and col. 6, line 61 - col. 7, line 6) and Cornils et al (fig. 1, and col. 3, line 58 - col. 4, line 34) as disclosing systems wherein reactor feed is preheated and fed to the reactor where feeds are mixed and cooled, which, the Examiner contends, reads on the apparatus of the present application. The Examiner further contends that it would have been obvious to a person of ordinary skill in the art to which the present invention relates at the time the present invention was made, to adapt the above mentioned features of Stephenson et al and/or Cornils et al to the apparatus of

Ashmead et al, thereby allegedly arriving at the same apparatus as that of the present application.

With respect to original claim 7, the Examiner points out that the claim does not recite any additional structural limitations, since recitation of the nature of the workpiece does not act as a limitation on the apparatus, and therefore the claim also reads on Ashmead et al.

New claim 15 is presented so as to recite the subject matter of original claim 7 as a structural limitation on the apparatus by stating that the microstructured channels and partial flow paths of the at least one closed, multifold, winding flow path of the miniaturized temperature-zone flow reactor are sufficiently large so as to accommodate a volume of reactants fed to the reactor that are mixed together with a volume of a carrier that is chemically non-miscible with the reactants, for transport through the reactor.

With regard to original claims 3 and 4 of the present application, the Examiner has stated that Ashmead et al further discloses that when the device is used in a bioreaction, a polymer is used on the laminae (Ashmead et al at col. 3, lines 14 - 18).

Finally, with regard to original claim 5 of the present application, the Examiner has stated that Ashmead et al further discloses that a lamina can be fabricated of glass (Ashmead et al at col. 3, lines 12 - 14).

With regard to all of the foregoing substantive rejections of the original claims as being obvious in view Ashmead et al in further view of any of the Stephenson et al, Peterson, and Cornils et al references, Applicants respectfully point out that none of the apparatus disclosed in the latter three of those references relates to a miniaturized temperature-zone flow reactor as is the apparatus of the present application. Therefore, the technology of those references is either not adaptable to the miniaturized reactor of the present application, or, at least, it would not have been obvious to a person of ordinary skill in the art of miniaturized bio-reactors, which is the field of art to which the apparatus of the present application pertains, at the time that the present invention was made, to utilize elements from large, macro-scale, commercial sized equipment and processes for ordinary, non-biological chemical reactions in a miniaturized bio-reactor.

Applicants respectfully point out that the technology and considerations underlying micro-scale bio-reactions, such as the polymerase chain reactions (PCR) in which sequences of DNA are amplified, as are capable of being performed using the apparatus of the present application, are completely different any of the disclosure in Stephenson et al, Peterson, and/or Cornils et al.

Accordingly, it is requested that all of the rejections of the original claims in the present application as being obvious over Ashmead et al in view of any one

of the three foregoing references should be removed, and should not be applied to any of the new claims in the present application after entry of this Amendment.

With regard to any of original claims 1, 2, 6, and 8 of the present application which were rejected in view of Ashmead et al alone, Applicants respectfully submit that although the apparatus of Ashmead et al relates to a miniaturized reactor, nevertheless, the apparatus of that reference is different from that of the present application, both as recited according to any of original claims 1, 2, 6, and/or 8, and to any of new claims 9 - 19.

Applicants respectfully point out that a feature of the apparatus of the present application that is not found in the apparatus of Ashmead et al is that with the apparatus of the present application, it is not necessary to provide, by expensive microtechnical methods, within individual chips, either thermally homogenous regions, or zones with steep temperature gradients, the latter of which would require the etching of deep channels in a silicon or metal substrate material, such as in the apparatus of Ashmead et al, or alternatively, which could be accomplished by membrane techniques, either of which process is extremely costly.

In contrast, according to the apparatus of the present application, reactor temperatures are determined and controlled by setting local thermal conductivity conditions in the reactor, which is accomplished very simply and relatively much less costly, by utilizing a connecting chip made from a material of low thermal



conductivity, such as pyrex glass, for areas within the reactor where there are high temperature gradients; and by utilizing substrate chips of a material of high thermal conductivity, such as silicon, for areas within the reactor requiring maintenance of homogeneous temperatures; and by the overall arrangement of combinations of such chips to control the entire overall temperature profile of a reaction as the reactants proceed through the flow paths and channels in these chips.

The use of materials of different thermal conductivities and the arrangement of chips of such materials in various combinations to control the temperature in a micro-sized bio-reactor is not taught, disclosed, or suggested by Ashmead et al.

Accordingly, it is requested that the rejections of original claims 1, 2, 6 and/Or 8 of the present application as being obvious over Ashmead et al be withdrawn, and that such rejections not be applied to any of new claims 9 - 19 entered by the present Amendment.

For the foregoing reasons, also, the rejections of the other original claims in the present application that were rejected in view of Ashmead et al in combination with any of the Stephenson et al, Peterson, or Cornils et al references should also be withdrawn because Ashmead et al itself does not provide a basis for an obvious type rejection. Also, because the apparatus of the present application, as recited according to new claims 9 - 19 of the application, present after entry of this Amendment, patentably distinguish over Ashmead et al, either taken alone or

in any combination with any of Stephenson et al, Peterson, or Cornils et al, the rejections should not be applied to any of the new claims.

In light of the foregoing, the application is now believed to be in proper form for allowance of all claims and notice to that effect is earnestly solicited.

No claims in excess of the number of claims previously paid for are added by the present Amendment, therefore, no additional claims fees are presently due.

Applicant respectfully requests a one month extension of time for responding to the Office Action. Please charge the fee of \$110.00 for the extension of time to Deposit Account No. 10-1250.

No other fees are believed due with the filing of this Amendment, however, if any other fees should be due, or if Applicants are entitled to any refunds of overpayments previously made, they should be respectively charged or credited to Deposit Account No. 10-1250.

Respectfully submitted,

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